Review Article

The evolution of the therapeutic strategy in hepatitis C: Features of sofosbuvir and indications

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A R T I C L E   I N F O

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The treatment of chronic hepatitis C virus infection is rapidly evolving with the entry into the therapeutic armamentarium of a series of new and highly effective direct antiviral agents, targeted to the different virus structures involved in hepatitis C virus replication and assembly. Sofosbuvir is considered, without controversies, the most promising single direct antiviral agent in the current scenario. The pharmacological properties of sofosbuvir allow a single oral daily administration and ensure a favourable drug–drug interaction profile, compared to other direct antiviral agents. Clinical development of sofosbuvir has been conducted with the strategy of positioning it as the backbone drug of several combination regimes, including triple therapy with pegylated interferon and ribavirin, but also IFN-free regimen with ribavirin alone as well as with complementary direct antiviral agents directed against other virus targets. Based on available data and International guidelines sofosbuvir is indicated in combination with pegylated interferon and ribavirin in patients infected with hepatitis C virus 1 to 6 that can take interferon, and this regimen is particularly efficacious in those who have not received any previous antiviral treatment. The pangenotypic activity, excellent safety (even in advanced liver disease) make sofosbuvir the ideal backbone for combination therapy in all hepatitis C virus patients subgroups, the limiting factors being safety and tolerability of the combined direct antiviral agent rather than those of sofosbuvir itself.

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1. Background

Hepatitis C represents a leading healthcare challenge in many parts of the world, being one of the leading causes of cirrhosis, of end-stage liver disease and of hepatocellular carcinoma. Chronic HCV infection associates with a significant medical and economic burden that is estimated will rise further in the coming years in the absence of an effective strategy of control and treatment interventions [1,2].

Treatment of chronic HCV infection with PEG-IFN and ribavirin, and more recently with PEG-IFN plus ribavirin and first generation protease inhibitors (Telaprevir and Boceprevir) for HCV-1, have been the standard of care until recently. Although there is solid evidence that patients achieving a sustained virological response (SVR) with definitive virus eradication with these regimes have a clear clinical benefit on long term disease complications and survival, this favourable outcome is achieved only in a subgroup of patients and in a small minority of those with more advanced liver disease, which are in more evident and urgent need of cure [3,4]. Furthermore, side effects are frequent and may be severe in individual cases, and many patients cannot be initiated on therapy due to contraindications, or are reluctant to receive interferon. Therefore, the clinical effectiveness of these treatment has been extremely limited as to the control of the burden of the infection and disease in the infected population and there is an urgent need for better tolerated and more effective treatments, particularly for those patients for whom PEG-IFN is not an option, those with more advanced liver disease, and those who have already taken and failed available therapies. The recent development of a series of new direct antiviral agents (DAAs) directed against HCV target proteins used by the virus for replication and assembly, has opened a new era in the treatment of hepatitis C, with the concrete prospective of moving rapidly from IFN-based regimes towards all oral IFN-free combinations characterized by higher efficacy and improved tolerability and safety [5]. Sofosbuvir, a nucleotide HCV polymerase inhibitor with pangenotypic activity, represents the bridge between these two strategies and appears as the essential backbone of most future DAAs combinations due to its high antiviral potency, pangenotypic activity, high barrier to resistance, favourable pharmacokinetics and excellent tolerability and safety profile.

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2.1. Reason for non-structural ical registered polymerase other stage assemblyments occurs such as Sofosbuvir histidine. Mechanism of disease reflects clinical practice with the HCV replicon. It is used in the context of the viral RNA polymerase, which is the enzyme responsible for the replication of the HCV genome. The HCV polymerase is a RNA-dependent RNA polymerase with a crucial role in the synthesis of new RNA genomes of HCV. Sofosbuvir is phosphorylated to its active form in the hepatocytes, and this activation occurs via human cathepsin A, Carboxylesterase 1 and histidine triad nucleotide binding protein 1 (Fig. 1). The active compound then competes with natural nucleotides causing termination of HCV-RNA replication. The active triphosphate form of Sofosbuvir targets the highly conserved active site of the HCV polymerase, and for this reason Sofosbuvir has pan-genotypic antiviral activity, although with some differences in potency, which has been confirmed in vitro experiments using the HCV replicon system. Diphosphorylation of active Sofosbuvir produces inactive metabolites such as GS-331007, which are cleared mainly by the kidney.

Oral Sofosbuvir is absorbed rapidly, with a median time to peak concentration (T\text{max}) of 1 h (0.5–3 h). Pharmacokinetics data indicate that Sofosbuvir can be administered without considering food intake. Demographic variables, such as age, sex, BMI, race, advanced liver disease with cirrhosis, as well as concomitant medications have been shown not to affect, or to have only a marginal effect, on pharmacokinetics of Sofosbuvir and of its metabolite in HCV infected individuals. Pharmacokinetic data indicate that Sofosbuvir can be administered without dose adjustments in the presence of mild or moderate renal impairment (eGFR > 30 mL/min/1.73 m²). On the other hand, the use of Sofosbuvir with severe renal impairment or end-stage renal disease requiring haemodialysis is not recommended.

Studies conducted in patients with moderate hepatic impairment (Child–Pugh B cirrhosis) would indicate that Sofosbuvir is well tolerated in these patients with no need for dose modifications.

A major advantage of Sofosbuvir compared to most other DAsAs against HCV derives from the evidence that Sofosbuvir and its major metabolite are not metabolized by the cytochrome (CYP) P450 enzymes or by uridine diphosphate glucuronyltransferase (UGT) and therefore do not cause any induction or inhibition of these enzymes. On the other hand, Sofosbuvir is a substrate of P-glycoprotein (Pgp) and of breast cancer resistance protein (BCRP) and therefore drugs or substances which are inducers of these pathways should be suspected to affect Sofosbuvir metabolism and to reduce its therapeutic efficacy. This means, in practical terms, that certain anticonvulsants such as carbamazepine, phenytoin, phenobarbital, oxcarbazepine, and antimycobacterials such as rifampin, rifampin and rifapentine can decrease the concentration and therapeutic effect of Sofosbuvir and should not be coadministered.

As regards the antiretroviral agents used to treat HIV coinfected patients, available data indicate that no dose adjustment of Sofosbuvir and of most reverse transcriptase inhibitors is needed when these drugs are combined [8]. However, coadministration of Sofosbuvir with tipranavir/ritonavir is not recommended.

Most importantly for the clinical setting, coadministration of Sofosbuvir has no clinically significant effect on the pharmacokinetics of the immunosuppressive drugs commonly used in liver transplant patients, such as cyclosporine A and tacrolimus, and dose adjustments are not needed [9]. Finally, Sofosbuvir can be combined with daily methadone, without clinically significant drug–drug interactions (DDI) [10]. The same is true for oral hormonal contraceptives that can be used during Sofosbuvir-based treatment without interference with the antiviral activity while maintaining their contraceptive efficacy.

2.2. Resistance profile

The rapid rate of HCV replication, combined with a lack of error proofreading by the viral RNA polymerase, are associated with a high frequency of mutations in the HCV-RNA genome. This is reflected in the high degree of genomic diversity which typically characterizes the virus quasispecies in individual cases. Mutations which confer reduced sensitivity or resistance to HCV DAAs may pre-exist before the drug is administered and/or may emerge or be selected during therapy and may become the predominant species, if they possess adequate replication fitness. This may result in treatment failure, as seen in some patients treated with Boceprevir or Telaprevir in association with PEG-IFN and ribavirin. Sofosbuvir appears to have an excellent high barrier to resistance, clearly superior to that of all other non-nucleotide inhibitors, PIs and NS5A inhibitors developed or under development for HCV. This is mainly because Sofosbuvir is directed against a highly conserved, active site of the virus polymerase, which is essential for virus replication. In vitro exposure to Sofosbuvir has been shown to select the NS5B S282T mutation in GT1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a replicons. This mutation reduces the sensitivity of HCV to Sofosbuvir, but also significantly reduces HCV replicative fitness to 1–10% of that of the wild type virus. The S282T mutants remain fully sensitive to ribavirin, which should always be administered with Sofosbuvir in the absence of other combined DAAs, and this is expected to greatly limit the emergence of the poorly replicating strains resistant to Sofosbuvir [11]. Furthermore, S282T mutants remain sensitive to other classes of DAAs without cross-resistance. These data taken together indicate that Sofosbuvir has a high barrier to resistance, as confirmed in clinical studies [12].

In the phase II and phase III Sofosbuvir studies, virological resistance was extensively studied and characterized by analyzing mutations in the HCV NS5B gene using both standard population sequencing and deep sequencing, in order to detect even very low levels of potentially resistant mutations. In addition, HCV-RNA from

Fig. 1. Sofosbuvir metabolism. The drug is phosphorylated to its active form in the hepatocytes, and this activation occurs via human cathepsin A, Carboxylesterase 1 and histidine triad nucleotide binding protein 1.
patients showing mutations in NS5B were cloned into an in vitro replicon system and tested for any associated reduction in susceptibility to SOF. According to these studies, none of the patients treated with SOF in phase II or phase III trials experienced virological breakthrough during therapy. The NS5B S282T mutation was detected in only 1 patient with relapse. The mutation reversed to wild type 24 weeks after cessation of SOF. In phase III studies, no drug resistance or drug associated breakthrough was observed in any of the patients. None of those who relapsed had the S282T mutation by deep sequence analysis. Although other NS5B substitutions were detected, they were not associated with a phenotypic change in SOF or RBV sensitivity in vitro.

These data further confirm in a most solid manner the high barrier to resistance of SOF and indicate that the drug can be used in HCV infected patients, even in a simplified dual combination with RBV, without generating resistance, and this is true for all major HCV genotypes, including HCV-1a.

2.3. Place in therapy

Sofosbuvir has been evaluated in phase II and phase III clinical trials in combination with PEG-IFN and ribavirin, as well as in all oral regimens with ribavirin or combined with other DAAAs. The results of these studies are described in detail in another chapter of this supplement issue [13]. These studies clearly indicate that sofosbuvir represents a major advance in the treatment of hepatitis C, and the ideal backbone for IFN based and for IFN free regimens for HCV patients infected with any HCV genotype and suffering from any stage of liver disease. The European (EMA) labelling indications for SOF are summarized in Table 1.

2.4. International guidelines (Table 2)

The American Association for the Study of Liver Diseases (AASLD) was the first to develop guidelines for the use of SOF in clinical practice [14]. In these guidelines, different SOF containing regimens are recommended for different patient subgroups with different ratings of strength and quality of supporting evidence (Table 2).

### Table 1

The European (EMA) labelling indications for sofosbuvir treatment. Sofosbuvir is also listed in the European SmCP of simeprevir.

<table>
<thead>
<tr>
<th>Patient subgroups</th>
<th>Regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with HCV-1, 4, 5, 6 who are intolerant or have contraindications to PEG-IFN</td>
<td>SOF + RBV + PEG-IFN</td>
<td>12 weeks&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Patients with HCV-2</td>
<td>SOF + RBV</td>
<td>12 weeks&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Patients with HCV-3</td>
<td>SOF + RBV + PEG-IFN</td>
<td>24 weeks&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Patients listed for liver transplant</td>
<td>SOF + RBV</td>
<td>Up to liver transplantation</td>
</tr>
<tr>
<td>Patients infected with HCV1 or HCV-4, independently of previous treatment history</td>
<td>SMV + SOF (± RBV)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>12 weeks&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Abbreviations**: SOF, sofosbuvir; PEG-IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir.

<sup>a</sup> Including patients coinfected with HIV.

<sup>b</sup> SOF = 400 mg daily; RBV = 1.000–1.200 mg daily based on body weight <75 kg, ≥75 kg; PEG-IFN-2a = 180 μg once weekly or PEG-IFN-2b = 1.5 mcg/kg one weekly.

<sup>c</sup> Extension to 24 weeks to be considered in patients who have one or more factors which have been historically associated with reduced response to IFN-based therapy (including advanced fibrosis/Cirrhosis) high baseline HCV-RNA levels, Afro-American origin, IL28B non-CC, previous null response to PEG-IFN and RBV treatment.

<sup>d</sup> SMV + SOF to be used only in patients who are intolerant or ineligible for PEG-IFN containing therapies, and have an urgent need for treatment. RBV should be added or not based on the treating physician decision at the single patient individual level.

2.4.1. **SOF plus PEG-IFN plus RBV for 12 weeks (The Neutrino Regimen)**

This regimen is recommended with high levels of strength and quality (Class I, level A) for naïve and relapsed HCV-1 infected patients who are eligible for IFN, independently of the HCV-1 subtype and stage of liver disease. This same regimen is also indicated, with a lower strength and/or quality for several patient subgroups including: Naïve and relapsers patients with HCV-3, HCV-4 and HCV-5 or 6, previous non-responder patients with HCV-1, 2, 3, 4, 5, 6. Triple therapy with SOF plus PEG-IFN plus RBV for 12 weeks, followed by additional 12 weeks of PEG-IFN plus RBV was indicated even for patients who have failed triple therapy with Boceprevir or Telaprevir, although there are no data to support this indication.

2.4.2. **SOF plus RBV**

This simplified all oral regimen, given for only 12 weeks, is recommended with high levels of strength and quality (Class I, Level A) for either naïve or experienced HCV-2 patients. SOF plus RBV, but for 24 weeks, is instead indicated for HCV-3 and for IFN-ineligible naïve HCV-1 patients and also for naïve and experienced IFN ineligible HCV-4, 5, and 6 patients. This same regimen is also considered a possible alternative option for HCV-1 patients who have failed triple therapy with BOC or TVR, but with no data to support it.

2.4.3. **SOF plus SMV with or without RBV**

This regimen is recommended for IFN ineligible and for experienced HCV-1 patients with Class I, level B.

The European Association for the study of the Liver (EASL) also produced updated Guidelines for the treatment of HCV in April 2014 [15]. These guidelines consider the use of SOF in combination with PEG-IFN and RBV, as well as in all oral combinations with RBV, with Simeprevir, and with Daclatasvir.

The EASL guidelines list a number of alternative options for the treatment of the different patient categories, giving the level of strength and quality of supporting evidence for each option.

As regards SOF-based regimens, the European guidelines give the following indications.

2.4.4. **SOF plus PEG-IFN plus RBV for 12 weeks**

Indicated for HCV-1 infected patients, if eligible for PEG-IFN and RBV, independently of HCV-1 subtype, previous therapy, and stage of liver disease (A1). The same regimen is also indicated for HCV-3 (A2) HCV-4 (B1) and HCV-5, 6 (B1). This regimen can also be considered as a possible alternative for HCV-2 patients with cirrhosis.

2.4.5. **SOF plus RBV for 12 weeks**

Indicated as the treatment of choice for HCV-2, with the possible extension to 16–20 weeks in patients with cirrhosis, particularly in those who have failed PEG-IFN plus ribavirin combination therapy.

2.4.6. **SOF plus RBV for 24 weeks**

May be used in HCV-1 infected patients who are intolerant or have contraindications for PEG-IFN, but only in the absence of availability of other, more efficacious, IFN-free regimens.

It is also suggested for HCV-3, but with the warning that it might be suboptimal in patients with cirrhosis who have failed PEG-IFN plus ribavirin combination therapy.

This same regimen is also indicated for HCV-4, 5, 6 infected patients who are intolerant or have contraindications for PEG-IFN (low strength and quality).

2.4.7. **SOF plus SMV for 12 weeks**

This regimen is indicated for HCV-1 and HCV-4 infected patients, the addition of ribavirin should be considered in patients with cirrhosis or with previous failure to achieve SVR with PEG-IFN and RBV.
### Table 2

**SOF-based regimens from International guidelines.**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Place in therapy</th>
<th>Quality of evidence/strength of recommendations[^a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF + RBV × 12 weeks</td>
<td>EASL HCV-2 (Naives and Experienced)</td>
<td>I/A</td>
</tr>
<tr>
<td></td>
<td>AASLD HCV-2 (Naives and Experienced)</td>
<td>A/B</td>
</tr>
<tr>
<td></td>
<td>AASLD HCV-3 Non responders</td>
<td>I/B</td>
</tr>
<tr>
<td></td>
<td>AASLD HCV-1 Naives (IFN ineligible)</td>
<td>IIa/A</td>
</tr>
<tr>
<td></td>
<td>AASLD HCV-4 Naives (IFN ineligible)</td>
<td>IIb/B</td>
</tr>
<tr>
<td></td>
<td>AASLD HCV-5/6 Experienced</td>
<td>IIa/C</td>
</tr>
<tr>
<td></td>
<td>AASLD HCV-3 Experienced</td>
<td>No data</td>
</tr>
<tr>
<td></td>
<td>EASL HCV-1 Naives/Experienced (only if IFN-non eligible, urgent and in the absence of better alternatives)</td>
<td>B/2</td>
</tr>
<tr>
<td></td>
<td>EASL HCV-4 Naives/Experienced (only if IFN-non eligible)</td>
<td>C/2</td>
</tr>
<tr>
<td></td>
<td>EASL HCV-5/6 Naives/Experienced (only if IFN-non eligible)</td>
<td>C/2</td>
</tr>
<tr>
<td></td>
<td>AASLD HCV-1 Naives</td>
<td>I/A</td>
</tr>
<tr>
<td></td>
<td>AASLD HCV-2 Experienced</td>
<td>IIa/B</td>
</tr>
<tr>
<td></td>
<td>AASLD HCV-3 Experienced</td>
<td>IIa/A</td>
</tr>
<tr>
<td></td>
<td>AASLD HCV-4 Experienced</td>
<td>IIa/B</td>
</tr>
<tr>
<td>SOF + Peg-IFN + RBV × 12 weeks</td>
<td>EASL HCV-4/5/6 Experienced</td>
<td>IIb/C</td>
</tr>
<tr>
<td></td>
<td>EASL HCV-1 Naives/Experienced</td>
<td>A/1</td>
</tr>
<tr>
<td></td>
<td>EASL HCV-2 Cirrhotics/Experienced</td>
<td>B/1</td>
</tr>
<tr>
<td></td>
<td>EASL HCV-3 Naives/Experienced</td>
<td>A/2</td>
</tr>
<tr>
<td></td>
<td>EASL HCV-4 Naives/Experienced</td>
<td>B/1</td>
</tr>
<tr>
<td></td>
<td>EASL HCV-5/6 Naives/Experienced</td>
<td>B/1</td>
</tr>
<tr>
<td>SOF + RBV (with or without PEG-IFN) × 24 weeks</td>
<td>AASLD HCV-1 Who have failed Triple (BOC/TVR) Therapy</td>
<td>No data</td>
</tr>
<tr>
<td>SOF + SMV × 12 weeks (with or without RBV)</td>
<td>AASLD HCV-1 Naives (IFN-non eligible)</td>
<td>I/B</td>
</tr>
<tr>
<td></td>
<td>EASL HCV-1 Experienced</td>
<td>IIa/B</td>
</tr>
<tr>
<td></td>
<td>EASL HCV-4 Naives/Experienced</td>
<td>B/1</td>
</tr>
<tr>
<td>SOF + DCV × 12–24 weeks (with or without RBV)</td>
<td>EASL HCV-1 Naives (12 weeks)</td>
<td>B/1</td>
</tr>
<tr>
<td></td>
<td>EASL HCV-3 Experienced (24 weeks) (Including BOC/TVR failures)</td>
<td>B/1</td>
</tr>
<tr>
<td></td>
<td>EASL HCV-4 Naives (12 weeks)</td>
<td>B/2</td>
</tr>
<tr>
<td></td>
<td>EASL HCV-4 Experienced (24 weeks)</td>
<td>B/2</td>
</tr>
</tbody>
</table>

**Abbreviations:** SOF, sofosbuvir; PEG-IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; BOC, boceprevir; TVR, telaprevir.


### 2.4.8. SOF plus DCV for 12 (naives) or 24 (experienced) weeks

This regimen is indicated for HCV-1 infected patients, including those who have failed triple therapy with Boceprevir or Telaprevir plus PEG-IFN and RBV.

The same regimen is also indicated for HCV-3 (B1) and HCV-4 (B2) infected patients.

### 2.5. From guidelines to clinical practice

The role of SOF in the treatment of chronic hepatitis C is expected to evolve rapidly, in this phase of great dynamic evolution in the treatment paradigms of the disease. The indication to when and how to use SOF in an optimized way is and will be closely dependent not only on the type of patient to be treated, but even more on the type of other DAA available for combination strategies. SOF represents the first, and still the most promising, oral agent against HCV and has the historical merit and strength of having permitted the switch from IFN-based to IFN-free regimens. Furthermore, considering the pangenotypic efficacy, and the resistance, safety and DDI profile, there is almost universal consensus that SOF is and will remain the ideal backbone drug for most IFN-free regimens. However, it should also be stated that some of the SOF-based regimens recommended by the most recent International Guidelines are not optimal and should therefore be used only in the absence of better options in patients in urgent need of treatment.

Based on available data from phase II and phase III clinical trials and from emerging evidence in clinical practice, the following considerations should guide physicians in the use of SOF to treat hepatitis C:

**HCV-1 infected patients:** The ideal regimen for these patients appears to be a combination of SOF with a complementary DAA. While awaiting the availability of the co-formulated SOF + Ledipasvir pill, the combination of SOF plus Simeprevir for 12 weeks seems to be the best choice for these patients, independently of HCV-1 subtype, previous treatments and stage of fibrosis. The exceptions are: patients who have failed triple therapy with Boceprevir or Telaprevir due to cross-resistance with Simeprevir; patients with severe liver impairment, due to uncertainty as to simeprevir pharmacokinetics and safety, and patients that need...
to take drugs with significant DDIs with Simeprevir. An alternative option for some of these patients is the combination of SOF with Daclatasvir, if there are no DDIs.

The triple regimen of SOF plus PEG-IFN and RBV for 12 weeks is an excellent strategy for naive HCV-1 patients that can take interferon, independently of the HCV-1 subtype and of stage of fibrosis. However, this regimen has not been tested in HCV-1 patients who have failed PEG-IFN and RBV, and although modelling by FDA has suggested that SVR could reach 71% in this setting, it seems reasonable to believe that this regimen could be adequate for relapsers, much less for partial responders and even less for null responders. Whether longer treatment duration could improve SVR in these difficult to treat patients is unknown, and therefore difficult to recommend.

The dual SOF+RBV oral combination appears suboptimal in most, if not all, HCV-1 patient categories in terms of achieving virus eradication, while it is relatively effective in achieving full suppression of HCV replication on therapy, even long term, due to the high barrier to resistance. This allows the achievement of complete HCV-RNA negativity in serum in patients on the liver transplant waiting list and efficiently prevents HCV recurrence after transplant in patients who receive the allograft after having undetectable serum HCV-RNA for at least 4 weeks. Whether long-term suppression of HCV replication by the combination of SOF plus RBV can also stabilize/improve patients with advanced, decompensated cirrhosis remains to be better clarified by ongoing studies, but this strategy will most likely be substituted in the near future by more effective DAA combinations, and this should be expected particularly for patients with HCV-1. It should be mentioned, however, that the combination of SOF plus RBV for 24 weeks has given excellent SVR rates in HCV-1 naïve patients infected with HIV, suggesting that this strategy could be a valid option in this setting, where addition of a second/third DAA could be problematic due to several drug–drug interactions.

HCV-2 infected patients: In these patients there is clear evidence that the combination of SOF + RBV is an excellent option, and superior to all other available options in terms of efficacy, tolerability and safety. Guidelines recommend the prolongation of therapy to 16–20 weeks in patients with cirrhosis and/or previous failure with PEG-IFN plus RBV. In these patients a triple regimen with SOF plus PEG-IFN plus RBV for 12 weeks should also be considered, when the patient is still eligible for PEG-IFN.

HCV-3 infected patients: Based on available data, these patients can be treated with SOF plus PEG-IFN plus RBV for 12 weeks or with SOF+RBV for 24 weeks. The former regimen should be preferred in patients that are still eligible for PEG-IFN, particularly cirrhotics or with previous failure to respond to PEG-IFN plus RBV. However, in the most difficult to treat HCV-3 patients, these regimens remain suboptimal and the combination of SOF plus DCV, if available, should also be considered.

HCV-4 infected patients: These patients can be treated with SOF plus PEG-IFN plus RBV for 12 weeks or with SOF plus RBV for 24 weeks. These regimens are adequate for naïve patients, independently of liver disease stage. Little data is available for patients that have failed PEG-IFN plus RBV, and in these cases the combination of SOF with SMV (or DCV) should be preferred, if these drugs are available.

HCV-5,6 infected patients: There are limited data with SOF, as well as with any other HCV DAA, in these rare HCV genotypes. The regimen of SOF plus PEG-IFN plus RBV for 12 weeks and, in alternative, SOF plus RBV for 24 weeks seems adequate, at least for naïve patients, until more data is available from trials and clinical practice.

3. Conclusions and perspectives

Sofosbuvir is a potent, HCV pangenotypic DAA with a high barrier to resistance and ideal DDIs and safety profile, which has ushered in a new era in the treatment of hepatitis C, as the first drug that can be used to cure HCV infected patients without IFN. The simplified SOF plus RBV combination is highly efficacious in HCV-2 patients when given for only 12 weeks. This same combination, given for 24 weeks, has been shown to provide benefits also in patients infected with other HCV genotypes, such as HCV-3, HCV-1 and HCV-4. In these patients, however, optimized IFN-free use of SOF requires its combination with a second complementary DAA, such as Simeprevir, Daclatasvir or Ledipasvir, depending on the HCV genotype. In this respect, SOF is and will certainly remain in the near future the fundamental backbone of the most effective, safe and easy to use IFN-free regimens to cure the different categories of HCV-infected individuals.

Conflict of interest

Professor Alfredo Alberti has received honoraria and research grants support from: GILEAD, ABBVIE, MERCK, ROCHE, JANSSEN, BMS, TIBOTEC. Dr. Sara Piovesan has received honoraria from: ABBVIE.

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